REMARKS/ARGUMENTS

Upon entry of this amendment, claims 1-18 are pending in the application. Claims 1, 4, 10 and 13 have been amended. Claims 2-3, 5-6, 8, 11-12, 14-15 and 17 have been canceled without prejudice. Claim 18 is new. Entry of the amendment, reconsideration of the rejection, and allowance of claims 1, 4, 7, 9-10, 13, 16 and 18 are respectfully requested.

The Amendment

In order to expedite prosecution of the application and advance the case toward allowance, the claims have been amended. No new matter was added by the amendment.

The specification has been amended to correct a number of informalities.

Claim 1 has been amended to specify that the MCP-1 receptor polypeptide comprises SEQ ID NO: 2 or SEQ ID NO: 4. Support for this amendment can be found, for example, in original claim 2 and in the specification, paragraphs 0033-0036. In addition, the term "binding fragment thereof" has been deleted. However, the term "binding fragment thereof" is supported in the specification, for example, in paragraph 0018, wherein the MCP-1 antagonists (*e.g.*, antibodies) and fragments thereof are discussed.

Claim 10 has been amended to specify that the method is a method for inhibiting MCP-1 receptor activation, wherein the method comprises administering to a patient a therapeutically effective amount of an MCP-1 receptor antagonist in a suitable pharmaceutical carrier, wherein the MCP-1 receptor antagonist is an antibody which binds to SEQ ID NO: 2 or SEQ ID NO: 4. Support for this amendment can be found in original claim 11 and in the specification, paragraphs 0033-0036. Support for inhibiting MCP-1 receptor activation can be found in the specification, for example, in paragraph 0128.

Claims 4 and 13 have been amended to correct for proper dependency.

Claim 18 is new and indicates that the antibody can be a Fab antibody fragment. Claim 18 is supported, for example, in paragraph 0015 of the specification. Paragraph 0015 incorporates by reference a number of publications that are well known in the art including *Methods in Enzymology,* Volumes 154 and 155 (Wu and Grossman, and Wu, Eds., respectively), (Mayer and Walker, Eds.) (1987); *Immunochemical Methods in Cell and Molecular Biology*

(Academic Press, London), Scopes, (1987); and *Handbook of Experimental Immunology,* Volumes I-IV (D. M. Weir and C. C. Blackwell, Eds 1986). For example, a binding fragment such as a Fab antibody fragment is supported on page 11.2 and throughout Chapter 14, pages 14.1-14.23 of Volume 1 of the *Handbook of Experimental Immunology,* (D. M. Weir and C. C. Blackwell, Eds 1986) which is incorporated by reference into the specification. Copies of the specific pages of the supporting references are attached hereto as Appendix A. As indicated above, the term "binding fragment" is also supported, for example, in paragraph 0018, wherein the MCP-1 antagonists (*e.g.,* antibodies) and fragments thereof are discussed.

Priority

The Office Action alleges that this application adds additional disclosure not presented in prior applications. However, the specification of this application is identical to the specifications of the prior filed U.S. Application Nos. 09/625,573 (filed 7/25/00) and 08/446,669 (filed 5/25/95) as well as the 371 National Stage Application PCT/US95/00476 (filed 1/11/95). The PCT/US95/00476 Application is a CIP of U.S. Application No. 08/182,962 which was filed on January 13, 1994. As such, the earliest priority date of this application is January 13, 1994.

Objection to the Drawings

The Applicants gratefully acknowledge that the objection to the drawings has been withdrawn.

Objection to the Specification

The disclosure is objected to because of minor informalities. The specification has been corrected accordingly (see amendment section).

Objection to the Claims

The Office Action indicates that if claims 1 or 10 are found allowable, then claims 3 and 6 and claims 12 and 15, respectively, will be objected to under 37 C.F.R. §1.75 as substantial duplicates thereof.

Claims 3, 6, 12 and 15 have been canceled. Thus, this objection is moot.

Rejections Under 35 U.S.C. §112

Claims 1-4, 6-13 and 15-17 are rejected under 35 U.S.C. §112, first paragraph, as being allegedly not enabled. The Examiner states that the specification is enabling for a method of administration of anti-MCP-1 receptor antibodies but is allegedly not enabling for inhibition of any condition characterized by monocytic infiltrates. Specifically, the Examiner indicates that the specification is only deemed enabling for intact antibodies which bind to the full length MCP-1 receptor with either SEQ ID NO: 2 or SEQ ID NO: 4.

The rejection is respectfully traversed.

However, in order to advance the case towards allowance, the claims have been amended to specify that the antagonist is an antibody which binds to a MCP-1 receptor comprising SEQ ID NO: 2 or SEQ ID NO: 4. Newly added dependent claim 18 specifies that the antibody can be a Fab antibody fragment. For the sake of completeness, the Applicants will address the Examiner's concerns.

First, the Examiner alleges that the specification does not provide guidance as to how to make fragments of antibodies which bind to MCP-1 receptor and are sufficient to inhibit conditions characterized by monocytic infiltrates. Herein, the Examiner argues that the specification does not disclose a relationship between particular structural elements of the MCP-1 receptor and the desired function of inhibiting the MCP-1 receptor, *i.e.,* which regions of the receptor must be bound in order for the claimed method to work. The Examiner indicates that the MCP-1 receptor is a complex molecule with seven transmembrane domains and there is allegedly not enough guidance to allow the skilled artisan to conclude that antibodies which bind the transmembrane domain, for example, will inhibit conditions characterized by monocytic infiltrates. The Examiner appears to suggest that it would have been difficult if not impossible to raise antibodies capable of inhibiting the MCP-1 receptor activation or monocytic infiltration. To the contrary, raising and testing antibodies was a routine procedure at the time of the invention. As described in *Wands*, a "considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance

with respect to the direction in which experimentation should precede." *Wands*, 8 USPQ2d at 1404 (quoting *In re Jackson,* 217 USPQ 804 (Bd. Pat. App. & Int. 1982). In addition, paragraph 0015 incorporates by reference several publications well known in the art that teach methods for raising antibodies against a variety of proteins. For example, methods of raising and characterizing antibodies is taught on pages 108.2-108.5 of Chapter 108, Volume 4 of the *Handbook of Experimental Immunology,* (D. M. Weir and C. C. Blackwell, Eds 1986) (see Appendix B) and throughout Chapter 13, pages 13.1-13.13, of Volume 1 of the *Handbook of Experimental Immunology,* (D. M. Weir and C. C. Blackwell, Eds 1986) (see Appendix C).

The Examiner is reminded that the courts have repeatedly held that a "patent need not teach, and preferably omits, what is well known in the art" (*Lindemann Maschinenfabrik GMBH v. American Hoist and Derrick Company et al.,* 221 USPQ 481 (Fed. Cir. 1984)). In fact, recent case law reemphasizes that the inventor must not teach what is already known in the art. In *Chiron Corporation v. Genentech Inc.* (363 F.3d 1247, 70 U.S.P.Q.2d 1321 (Fed. Cir. 2004)), the Federal Circuit held that "a patent disclosure need not enable information within the knowledge of an ordinarily skilled artisan. Thus, a patentee preferably omits from the disclosure any **routine** technology that is well known at the time of application." (Citing *Hybritech,* 802 F.2d at 1384.) [Emphasis added.]

As the Examiner must surely know, antibodies are generally raised to the entire protein of interest. It was well known at the time of the invention how to raise antibodies to the entire protein and then test which antibodies provide the desired function *(e.g.,* inhibition of activation). At the time of the invention, testing antibodies for a variety of functions did not require undue experimentation. Indeed, the Applicants teach methods for using antibodies capable of inhibiting the receptor function, *e.g.,* see the antagonist assays discussed in paragraphs 0017, 0018, 0028 and 0083 through 0086. Moreover, the Examiner is referred to Appendices B and C, wherein it is shown that antibodies can be easily made and tested.

The Examiner's suggestion that the specification does not disclose a relationship between particular structural elements of the MCP-1 receptor and the desired function is not relevant since it is not required in order to raise functional antibodies. As pointed out above, antibodies are routinely raised to the entire protein and thus, a discussion of the relationship

between structural elements of the receptor and the desired function is not necessary. Besides, the structure and function of the MCP-1 receptor is disclosed in the specification.

Second, the Examiner alleges that the Applicants have not provided sufficient guidance as to which fragments of antibodies can be used in the present method. Notably, the Examiner acknowledges on the record that the art recognizes that Fab fragments are well known. However, the Office Action indicates that claims 1, 6, 10 and 15 recite the limitation "binding fragment thereof" which is allegedly of a different scope than Fab fragments.

The claims have been amended to recite antibodies which bind to a MCP-1 receptor comprising SEQ ID NO: 2 or SEQ ID NO: 4. The term "antibody" would have been understood by those of skill in the art at the time of the invention to encompass several different binding entities including Fab antibody fragments, Fc antibody fragments, monoclonal antibodies, polyclonal antibodies, *etc.* For example, the skilled artisan would have been well aware that a Fab antibody fragment contains the antigen-binding site and is generated by cleavage of the antibody with an enzyme (*e.g.,* papain). In fact, as acknowledged by the Examiner, the use of an antibody or Fab antibody fragment thereof was considered a routine procedure at the time of filing. Notably, all the terms referred to in the claims (*e.g.,* monoclonal antibody, Fab antibody fragment, *etc.*) are clearly understood by anyone of average skill in the art to be included in the term antibody. Hence, the Applicants are not required to teach what is well know in the art such as routine methods of isolating and making antibodies and/or Fab antibody fragments specific for the MCP-1 receptor in order to inhibit binding of MCP-1. Also, the newly added dependent claim 18 specifies that the antibody can be a Fab antibody fragment. As indicated previously, support for a binding fragment such as a Fab antibody fragment can be found, for example, on page 11.2 and throughout Chapter 14, pages 14.1-14.23 of Volume 1 of the *Handbook of Experimental Immunology,* (D. M. Weir and C. C. Blackwell, Eds 1986) which is incorporated by reference into the specification in paragraph 0015.

Third, the Examiner alleges that the specification does not provide sufficient guidance to allow a skilled artisan to know how to identify conditions characterized by monocytic infiltrates.

To the contrary, the specification provides a number of examples of diseases that are characterized by monocytic infiltrates such as atherosclerosis, rheumatoid arthritis, cancer and alvcolitis (see paragraph 0028). The skilled artisan would not have to engage in undue experimentation in order to find out *which* conditions are characterized by monocytic infiltrates. Besides, the art provided sufficient teachings about conditions that are characterized by monocytic infiltrates at the time of the invention. Indeed, the background section of the invention emphasizes the clinical aspect of MCP-1 and teaches on page 2, paragraph 0006 that MCP-1 was reported to activate monocyte-mediated tumoristatic activity and to induce tumoricidal activity (see, *e.g.,* Rollins, *Mol. and Cell. Biol.* 11:3125-31(1991) and Walter, *Int. J. Cancer* 49:431-35(1991)). The background section further teaches that MCP-1 has been implicated as an important factor in mediating monocytic infiltration of tissues inflammatory processes such as rheumatoid arthritis and alveolitis (see, *e.g.,* Koch, *J. Clin. Invest.* 90:772-79 (1992) and Jones, *J. Immunol.* 149:2147-54 (1992)) and that it may also play a fundamental role in the recruitment of monocyte-macrophages in developing atherosclerotic lesions (see *e.g.,* Nelken, *J. Clin. Invest.* 88:1121-27 (1991), Yla-Herttuala, *Proc. Nat'l. Acad. Sci.* USA 88:5252-56 (1991) and Cushing, *Proc. Natl., Acad. Sci.* USA 87:5134-38 (1990)).

In addition, Rollins (see *Mol. Med. Today* 2(5):198-204 (1996); enclosed for the Examiner's convenience) taught in 1996 that MCP-1 has been implicated in diseases characterized by monocyte-rich infiltrates, including atherosclerosis, rheumatoid arthritis and multiple sclerosis, and that data from genetically modified mice suggests an important role for MCP-1 in monocyte trafficking and activation. Although, Rollins was published after the filing date of the invention, it further emphasizes that MCP-1 is involved in monocytic infiltration which is consistent with the teachings of the invention. Most importantly, the specification teaches in paragraph 0008 that antagonists (*e.g.,* antibodies) are excellent candidates for therapeutics for the treatment of atherosclerosis in tumor growth suppression and in other diseases characterized by monocytic infiltrates such as rheumatoid arthritis and alvcolitis.

The Examiner must appreciate that it was the Applicants who first discovered that the MCP-1 receptor can be inhibited in order to treat conditions related to monocytic infiltrates such as atherosclerosis and rheumatoid arthritis. The specification teaches in

paragraph 0017 that the invention provides compositions for use in therapy, diagnosis, and assays specific to the MCP-1 receptor. This includes raising antibodies to the MCP-1 receptor. The invention also provides an assay to assess MCP-1 binding, useful in screening for specific antagonists (*e.g.,* antibodies) of the MCP-1 receptor. Such an assay includes the steps of expressing and isolating the recombinant MCP-1 receptor and/or the extracellular domains which permits the development of therapeutic antagonists, useful in the treatment of atherosclerosis and other diseases characterized by monocytic infiltrates. In fact, paragraph 0136 of the specification also states that early atherosclerotic lesions have a predominantly monocytic infiltrate and MCP-1 is abundant in these lesions. In light of this guidance, the skilled artisan should find no difficulty in using the teachings of the invention and the information known in the art in order to practice inhibiting the MCP-1 receptor via an antibody in order to inhibit conditions characterized by monocytic infiltrates.

Fourth, the Office Action asserts that claims 1 and 10 both recite the limitation "therapeutically effective amount" and that the skilled artisan would have to resort to undue experimentation just to find which conditions are characterized by monocytic infiltrates and to determine a therapeutically effective amount of the antibody to be administered. Furthermore, the Office Action alleges that the art recognizes that the treatment of diseases with antibodies is unpredictable, citing Harris *et al.* (1993).

The "test of enablement is not whether any experimentation is necessary, but whether, if experimentation is necessary, it is undue" (*In re Angstadt,* 537 F.2d 498, 504, 190 USPQ 214, 219 (CCPA 1976).

The specification provides a clear definition in paragraph 0084, wherein *an effective amount* is a concentration sufficient to block the binding of MCP-1 to the receptor domain. This loss in binding of MCP-1 to the receptor can be first tested using various techniques, such as intact cells or in solid-phase assays (see paragraphs 0122-0138). Then the specification provides an example of a therapeutically effective amount of an antagonist in paragraph 0090. Paragraph 0090 teaches that the term "therapeutically effective amount" means the total amount of the active component of the method or composition that is sufficient to show a meaningful patient benefit, *i.e.,* healing of the chronic condition or an increase in the rate of

healing. The specification states that a therapeutically effective dose of an antagonist composition of this invention is contemplated to be in the range of about 10 micrograms to about 1 milligram per milliliter per dose administered. Other than citing Harris *et al.* (1993), the Examiner has provided no evidence why the skilled artisan could not administer a therapeutically effective amount of an antagonist in the range provided, such as an antibody to a patient in order to block MCP-1 receptor binding and thereby affect conditions characterized by monocytic infiltrates such as, for example, atherosclerosis.

The questions is whether or not the skilled artisan can practice the invention as claimed without undue experimentation and not whether the treatment is necessarily equally effective in every single patient. The specification even states in paragraph 0089, that the amount of active ingredient will depend upon the severity of the condition, the route of administration, the activity of the antagonist, and ultimately will be decided by the attending physician. Notably, the final determination of the ultimate effectiveness of any drug or procedure is not the territory of the U.S. PTO but should be left to the FDA. The Applicants submit that the skilled artisan can practice the claimed invention without undue experimentation in light of the teachings provided in the specification and the general knowledge available in the art.

In light of the above amendment and remarks, it is respectfully requested that the rejection of claim 1-4, 6-13 and 15-17 under 35 U.S.C. §112, first paragraph, be withdrawn.

Claims 1-4, 6-13 and 15-17 are rejected under 35 U.S.C. §112, first paragraph, as allegedly lacking written description. The Office Action alleges that the instant disclosure does not adequately describe the scope of the use of "binding fragment thereof" because this is a broad generic term which encompasses a wide variety of antigen binding fragments.

This rejection is respectfully traversed.

As indicated above, the specification provides support for a "binding fragment", in paragraph 0018, wherein the MCP-1 antagonists (*e.g.,* antibodies) and fragments thereof are discussed. In addition, the claims have been amended to specify that the antagonist is an antibody which binds to a MCP-1 receptor comprising SEQ ID NO: 2 or SEQ ID NO: 4, and

newly added dependent claim 18 specifies that the antibody can be a Fab antibody fragment which is supported in the specification (*supra*). As a result, the rejection with respect to binding fragment should be moot.

The Office Action further asserts that the following recitations indicated below are not supported in the specification or priority documents. However, all the Examiner's recited terms find support in the specification and priority documents which is explained below:

A "binding fragment thereof" is supported in paragraph 0018, wherein the MCP-1 antagonists (*e.g.*, antibodies) and fragments thereof are discussed. Furthermore, antibody fragments like Fab antibody fragments are supported, for example, on page 11.2 and throughout Chapter 14, pages 14.1-14.23 of Volume 1 of the *Handbook of Experimental Immunology,* (D. M. Weir and C. C. Blackwell, Eds 1986) which is incorporated by reference into the specification in paragraph 0015 (see Appendix A).

The term "about 10 μg/ml to about 1 mg/ml" is supported in the specification, for example, in paragraph 0090. Paragraph 0090 discloses that a therapeutically effective dose of an antagonist composition of this invention is contemplated to be in the range of about 10 micrograms to about 1 milligram per milliliter per dose administered.

The term "monoclonal antibody" is supported in the specification, for example, in paragraph 0015. Paragraph 0015 lists a number of references that are well known in the art including *Methods in Enzymology,* Volumes 154 and 155 (Wu and Grossman, and Wu, Eds., respectively), (Mayer and Walker, Eds.) (1987); *Immunochemical Methods in Cell and Molecular Biology* (Academic Press, London), Scopes, (1987); and *Handbook of Experimental Immunology,* Volumes I-IV (D. M. Weir and C. C. Blackwell, Eds 1986). Specifically, the term "monoclonal antibody" is supported, for example, throughout Chapter 13, pages 13.1-13.13, of Volume 1 of the *Handbook of Experimental Immunology,* (D. M. Weir and C. C. Blackwell, Eds 1986). Copies of the specific pages of the supporting references are attached as Appendix C. The Examiner must appreciate that the term "monoclonal antibody" would have been clearly understood by those of skill in the art at the time of the invention. This information has been available to those of skill for a considerable period of time and the skilled artisan would certainly understand what the term "monoclonal antibody" encompasses. The Examiner is invited to

review the attached references from 1986 to see that the art was generally well informed about monoclonal antibodies and the methods of how to employ them.

The term "method for inhibiting MCP-1 receptor polypeptide" is supported in the specification, for example, in paragraphs 0122 to 0138. Claim 10 has been amended to specify that the method is a method for inhibiting MCP-1 receptor polypeptide activation. This is specifically supported, for example, in paragraph 0128. The Examiner has acknowledged that the specification provides support for the inhibition of the activation of the MCP-1 receptor, as measured with mobilization of intracellular calcium and activation of adenlylyl cyclase.

Finally, it is stated for the record that subject matter in the original and amended claims finds support in the specification and priority documents as shown above. No new matter was added to the application.

In light of the above amendment and remarks, it is respectfully requested that the rejection of claim 1-4, 6-13 and 15-17 under 35 U.S.C. §112, first paragraph, be withdrawn.

Claims 1-4, 6-13 and 15-17 are rejected under under 35 U.S.C. §112, second paragraph, for being allegedly indefinite.

Specifically, the Examiner objects to the term "antibody or binding fragment thereof". The claims have been amended as shown above. In light of this amendment, this rejection is moot.

Rejection under 35 U.S.C. §102(b)

Claims 1-3, 6-12 and 15-17 are rejected under 35 U.S.C. §102(b), for allegedly being anticipated by La Rosa *et al.,* U.S. Patent No. 6,312, 689, as cited on the Applicants IDS.

The rejection is respectfully traversed. It is stated for the record that since La Rosa *et al.* was issued on November 6, 2001 and the instant application has a priority date of January 11, 1995, La Rosa *et al.* does not qualify as a reference under 35 U.S.C. §102(b).

Rejection under 35 U.S.C. §103(a)

Claims 4 and 13 are rejected under 35 U.S.C. §103(a), for allegedly being obvious over LaRosa *et al.*, U.S. Patent No. 6,312, 689.

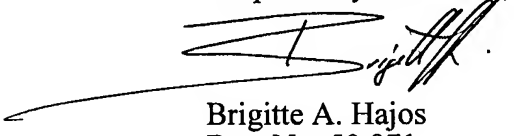
The rejection is respectfully traversed. As indicated above, La Rosa *et al.* was issued on November 6, 2001 and the instant application has a priority date of January 11, 1995. Thus, La Rosa *et al.* does not qualify as a reference under 35 U.S.C. §103(a) either.

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 415-576-0200.

Respectfully submitted,



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